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OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

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MEMORANDUM

DATE: December 13, 2000

SUBJECT: Atrazine: Evaluation of Carcinogenic Potential

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THROUGH: William Burnam, Chairman, Cancer Assessment Review Committee
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TO: Sanjivani Diwan, PhD
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Health Effects Division (7509C), Office of Pesticide Programs

This memorandum contains the conclusions from the seventh Health Effects Division (HED) Cancer Assessment Review Committee (CARC) meeting (December 13, 2000) subsequent to the sixth CARC meeting held in November 2000 (Memorandum, From Roger Hawks to Catherine Eiden, November 1, 2000). The conclusions from the November 1, 2000 meeting were considered provisional pending receipt and review of the written comments from the June 27th to 29th, 2000 FIFRA Scientific Advisory Panel (SAP) meeting which convened to consider a preliminary hazard and dose-response assessment for atrazine prepared by HED[1]. The final report of the June 27, 2000 SAP meeting is now available[2]. Thus, the purpose of the December 13, 2000 CARC meeting was to consider and revise, if necessary, and finalize provisional conclusions of the November 1, 2000 CARC meeting.

[1]see http://www.epa.gov.scipoly/sap/2000/june27finalparta_atz.pdf
[2]see http://www.epa.gov.scipoly/sap/2000/june27/finalatrazine.pdf

CARC members present:

Lori Brunsman

Joycelyn Stewart

Clark Swentzel

Mike Ioannou

Vicki Dellarco

Karl Baetcke

Virginia Dobozy

Marion Copley

Bill Burnam

Linda Taylor

Others present:
Cathy Eiden
(HED - nonvoting)

EXECUTIVE SUMMARY

At a meeting of the CARC held on December 13, 2000, atrazine was classified as "Not Likely To Be Carcinogenic To Humans" in accordance with the draft Guidelines for Carcinogen Risk Assessment (July, 1999). This decision was based on the information discussed below.

Atrazine is associated with mammary and pituitary tumors in female Sprague-Dawley (SD) rats, but not in male SD rats, or either sex of Fischer 344 (F-344) rats or CD-1 mice. Mutagenic and estrogenic activity do not appear to play a significant role in atrazine-associated carcinogenicity. Biological plausibility has been established for the mode of carcinogenic activity of atrazine. The rat cancer mode of action (MOA) involves a process consisting of modulation of the gonadotrophin releasing hormone (GnRH) pulse, attenuation of pituitary releases of luteinizing hormone (LH), and alteration of ovulatory cycles, expressed as constant estrus, which leads to prolonged exposure of mammary and pituitary tissues to estrogen and prolactin, and development of tumors in response to the prolonged hormone exposures. This MOA essentially accelerates the normal aging process in female SD rats. It would be expected to be operative in other rat strains with a similar reproductive aging process (e.g. Long Evans and Wistar). Although atrazine might cause adverse effects on hypothalamic-pituitary function in humans, the hormonal environment conducive to tumor development (i.e., elevated or prolonged exposure to estrogen and prolactin) that is found in SD rats is not expected to occur in humans. Instead, humans respond to reduced LH by having reductions in estrogen and prolactin. Although possible associations between atrazine exposure and non-Hodgkins lymphoma (NHL) and ovarian cancer have been reported in a few epidemiology studies, there is no supporting evidence or a sound argument of biological plausibility that these cancers may result from exposure to atrazine. Also, the lack of multiple confirming studies indicates that the human investigations by themselves do not make a strong case for an association between atrazine exposure and human cancer.

I. INTRODUCTION

At the meeting of the CARC held on December 13, 2000, the final report of the Scientific Advisory Panel (SAP Report No. 2000-05) was considered along with the provisional conclusions reached in the previous meeting of the CARC (November 1, 2000). The major conclusions of the SAP were as follows:

1. High doses of atrazine cause an increased incidence and earlier appearance of mammary adenomas and carcinomas in female SD rats but not in female F-344 rats, male SD or F-344 rats, or CD-1 mice of either sex.

2. Atrazine's MOA for the development of mammary tumors has been demonstrated. The SAP pointed out the uncertainties in the MOA but concluded that the weaknesses and limitations have been adequately addressed and are not sufficient to raise doubt about the overall MOA.

3. Regarding the question of relevance of the MOA in rats to humans, the SAP concluded:

a) There are similarities in the control of the hypothalamic-pituitary-ovarian axis between

humans and rats but there are important differences. The MOA for mammary tumors in SD rats is an acceleration of the reproductive aging process in which decreased LH levels lead to prolonged exposure of mammary tissue to estrogen and prolactin. In contrast, reproductive aging (menopause) in human females is characterized by low levels of estrogen and high levels of LH and follicle stimulating hormone (FSH).

b) There was some concern about epidemiology studies demonstrating a possible increased risk of NHL and ovarian cancer associated with atrazine exposure. However, the Panel concluded there was not a strong association due to the lack of multiple studies and some inconsistencies in the reported studies.

c) The Panel concluded that hypothalamic amenorrhea (HA) and polycystic ovarian syndrome (PCOS), anovulatory conditions in human females proposed by EPA as possible correlates to the reproductive effects of atrazine in rats, present much different endocrine profiles than age-related persistent estrus in SD rats.

4. It was the consensus of the SAP that atrazine should be classified as either "Not Likely to be Carcinogenic To Humans" or "Not Enough Information to Classify". The Panel also concluded that the MOA for atrazine carcinogenicity is not applicable to developing fetuses and children.

A preliminary hazard and dose-response assessment that was presented to the SAP (June 27, 2000) concluded that atrazine should be classified as "Likely To Be Carcinogenic To Humans." The "Likely" cancer classification was proposed because there is some evidence in the literature that CNS-acting drugs, like atrazine, may disrupt the GnRH and LH pulses and lead to disruption of the menstrual cycle in primates and humans. Further, it was thought that conditions of anovulation in humans, although in several respects dissimilar to atrazine's mode of action in the SD female rat, raised uncertainties about the possible endocrine imbalance by this CNS mode of action. Therefore, it was proposed to the June 27th SAP that human relevance should be presumed. However, as noted above, the June 27th SAP expressed the view that the mode of carcinogenic action of atrazine is not expected to be operative in humans and that atrazine should not be classified as a "Likely" human carcinogen but that "it would be more appropriate to classify atrazine as either "Unlikely To Be a Human Carcinogen" or "Not Enough Information To Classify." At the November 1, 2000 CARC meeting, the view of the SAP was discussed and atrazine was reclassified, subject to review of the final SAP report, as "Not Likely To Be Carcinogenic To Humans." Below is a reconsideration of the November CARC conclusions in light of the SAP final report.

II. EVALUATION OF CARCINOGENICITY

In reaching a final decision on the carcinogenicity classification for atrazine, the committee considered the following information.

1. Data demonstrating an increased incidence and decreased time to onset of mammary and pituitary tumors in female SD rats, but not in male SD rats or F-344 rats or CD-1 mice of either sex.

2. Data on the proposed MOA associated with the carcinogenesis seen in female SD rats following atrazine exposure.

3. Comments provided in the final report of the SAP meeting of June 27, 2000 regarding the relevance of the MOA established for rat carcinogenicity to humans.

4. Evidence that mutagenicity and direct estrogenic activity do not play a significant role in atrazine-associated carcinogenicity.

5. Results of epidemiology studies that suggest an association between atrazine exposure and carcinogenicity in humans.

III. COMMITTEE'S ASSESSMENT OF THE WEIGHT OF EVIDENCE

The following factors were considered in evaluating the weight of evidence.

A MOA has been established for these mammary and pituitary tumors in female SD rats that is unlikely to be operative in humans. Previously the CARC classified atrazine as a "Likely" carcinogen and the draft document presented to SAP June 27, 2000 reflected this opinion. This classification assumed that a pair of human models of anovulatory conditions associated with aberrant GnRH pulses (PCOS and HA) were models of the above-described rat MOA in humans. The deliberations at the June SAP meeting clearly reflected the SAP's view that these two human models were not appropriate for comparison to the SD rat model and did not establish the human relevance for the proposed mode of action. GnRH pulse modulation of pituitary releases of LH is a central driver of ovulation in the SD female rat, and atrazine is essentially accelerating the aging process of the CNS control of ovulation, which leads to a constant state of estrus (anovulation), and prolonged exposure to estrogen and prolactin. As noted by the SAP, although there are certain similarities in the control of the hypothalamic-pituitary- ovarian axis between humans and rats in that the hypothalamus can play a key regulatory role in primates, there are fundamental differences. Unlike the SD rat, CNS modulation is not the driving factor on human GnRH and LH releases. The EPA preliminary atrazine hazard and dose-response assessment wrongly assumed that an increase in estrogen could result from an attenuation of the LH release in humans. Although human conditions of anovulation are associated with aberrant GnRH and LH pulsatile releases and even if atrazine induced anovulation in humans like in the SD rat, there is no evidence for the potential of an unopposed estrogen condition in humans that would lead to tumor development. It appears that in humans when LH is low, such as in HA, a state of low serum estrogen is found, not elevated or prolonged estrogen exposure. There is no known cancer risk associated with HA patients, albeit they are at risk to a number of other clinical conditions (e.g., osteoporosis, heart disease, infertility). Another condition of anovulation, PCOS, is also not a good model for atrazine cancer MOA in SD rats. The etiology of PCOS is multi factorial, and LH secretion is elevated due to increased synthesis of androgen and its conversion to estrogens. Although atrazine might cause adverse effects on hypothalamic-pituitary function in humans, the hormonal environment

conducive to tumor development (i.e., elevated or prolonged exposure to estrogen or prolactin) that is found in SD rats is not present in humans. Therefore, it is unlikely that atrazine's mode of cancer action in SD rats is operative in humans. The CARC agreed with the view reflected in the written comments of the June 2000 SAP review.

The human epidemiology database does not provide sufficient evidence to associate atrazine with human cancer of any tissue. The SAP report contains a discussion of issues regarding the Agency's evaluation of the human epidemiology data on atrazine and recommendations for further analyses of the data. Despite some of the short-comings pointed out by the panel, the panel stated that the summary paragraph on the evaluation of the human epidemiology in the Agency's assessment document should be revised to:

> "To summarize, there are a few epidemiological studies that suggest a possible association between atrazine (or triazine) exposure and NHL and ovarian cancer. However, lack of multiple studies available indicates that the human studies by themselves do not make a strong case for an association."

On closer evaluation since the June SAP meeting, the CARC agreed with the SAP that the human studies "by themselves do not make a strong case" for an association between atrazine exposure and a cancer risk. Although possible associations between atrazine exposure and NHL and ovarian cancer are reported, there is no supporting evidence or a sound argument of biological plausibility that these cancers may result from exposure to atrazine. Several two- year bioassays with atrazine in SD and F-344 rats, and CD-1 mice failed to show evidence of an increased incidence of ovarian tumors or lymphomas. Furthermore, ovarian cancer is associated with frequent ovulations (not anovulation) or stimulation by FSH and LH (not suppression of LH), thus increasing their exposure to estrogens (see Fathalla, M.F., 1971, Lancet 2 (7716):163; Cramer, D.W. and Welch, W.R., 1983, J. Natl. Cancer Inst. 71(4):717-21). NHL is associated with immune dysfunction and not hormonal imbalance.

IV. CLASSIFICATION OF CARCINOGENIC POTENTIAL

Following discussion of the conclusions reached at the November 1, 2000 CARC meeting and consideration of the comments and recommendations provided by the Scientific Advisory Panel, the December 13, 2000 CARC reaffirmed the classification of atrazine as "Not Likely To Be Carcinogenic To Humans" based on the overall weight of evidence that:

1. The mode of carcinogenic activity in the female SD rat is supported by the data.

2. The mode of carcinogenic activity in the female SD rat essentially involves an acceleration of the reproductive aging process.

3. The mode of action for the carcinogenicity of atrazine is unlikely to be expressed in humans; no human conditions can be established that support a potential for atrazine to lead to carcinogenicity in humans.

4. Other modes of action are not supported by the available data and, in particular, mutagenic and estrogenic activity do not appear to significantly contribute to atrazine's carcinogenic potential.

5. Although a few epidemiological studies suggest a possible association between atrazine (or triazine) exposure and NHL and ovarian cancer, these cancers do not appear to be plausible based on atrazine's mode of action. Therefore, the human studies by themselves do not make a strong case for an association.

The CARC agreed that a response to the SAP comments, the classification of atrazine as "not likely to be a human carcinogen", and the supporting weight of evidence for the classification should be incorporated in the atrazine hazard and dose-response assessment document when it is finalized.